Cognitive outcome in congenital central hypothyroidism: a systematic review with meta-analysis of individual patient data

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Abstract

Objective: To provide an overview of cognitive and motor outcome, and quality of life (QoL) in patients with congenital central hypothyroidism (CH-C).

Design: Systematic review with individual patient data (IPD) meta-analysis.

Methods: OVID MEDLINE, EMBASE and PsycInfo were searched from inception to June 11th, 2019. Studies in patients with CH-C, either isolated or with multiple pituitary hormone deficiency (MPHD), were included if CH-C patients could be separated from any additional patient groups. Primary outcomes were full-scale intelligence quotient (FSIQ) and motor outcome; secondary outcome was QoL. Following data-extraction, one-stage IPD meta-analysis was performed, fitting a linear mixed model with FSIQ as dependent variable. Random intercepts were fitted for each study.

Results: Six studies measuring FSIQ were eligible for meta-analysis, comprising 30 CH-C patients (20 males; 27 MPHD patients). FSIQ range was wide (64–123). Mean weighted FSIQ was 97 (95% CI: 88–105). Twenty-seven percent had an FSIQ below 85 (≥ 1 s.d. below norm score), and 10% below 70 (≥ 2 s.d. below norm score). There was no significant association between FSIQ and sex or age. Age at treatment initiation was available from three studies only, thus impeding a reliable analysis of this parameter. Motor outcome and QoL were each studied in one study; no quantitative analyses could be performed for these outcomes.

Conclusion: A wide range in FSIQ scores was observed in CH-C patients. Results should be interpreted with caution, because included patients mainly had MPHD and age at treatment initiation was unknown for the majority of patients.

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Introduction

Thyroid hormone is indispensable for normal pre- and postnatal brain development, and untreated congenital hypothyroidism (CH) leads to permanent intellectual and motor disability. Because early detection and treatment of CH prevents developmental disability, neonatal screening

programs for CH have been implemented worldwide since the late 1970s (1, 2).

CH may be of thyroidal (CH-T) or central, i.e. hypothalamic-pituitary, origin (CH-C). CH-T is much more prevalent than CH-C (1 per 3000 vs 1 per 16,000

live births) (3). Most neonatal screening programs aim at detecting CH-T and do not detect CH-C (4). Few countries use a screening program that detects both CH-T and CH-C, for example, the Netherlands, Israel and parts of Japan, Italy and the United States (4, 5, 6, 7, 8).

It can be hypothesized that CH-C and CH-T patients face a similar risk for developmental disability. Contrary to the frequent assumption that the severity of hypothyroidism is only mild in CH-C, we showed that more than half of CH-C patients have moderate-to-severe hypothyroidism in the neonatal phase, requiring immediate treatment to prevent brain damage (9). Furthermore, in approximately two thirds of patients CH-C is part of multiple pituitary hormone deficiency (MPHD) (10). MPHD provides an additional risk for developmental disability, because central adrenal insufficiency and/or growth hormone deficiency (GHD) may lead to brain damaging hypoglycemia and circulatory shock (4, 11). Finally, quality of life (QoL) may also be impaired, as has been observed in patients with CH-T, as well as in patients with childhood-onset hypopituitarism (12, 13).

Cognitive outcome of early treated CH-T patients has been studied extensively (2, 14, 15, 16, 17). However, outcome studies in both early and late treated CH-C patients are scarce, and an overview of studies is lacking. Furthermore, it remains unknown whether early detection by neonatal screening and subsequent early treatment of CH-C patients improves cognitive outcome when compared with late diagnosed and treated CH-C patients.

To provide an overview of the currently reported cognitive and motor outcomes, and QoL in CH-C patients, whether treated early or late, we conducted a systematic review and individual patient data (IPD) meta-analysis. For this review and meta-analysis we included both patients with isolated CH-C and patients with CH-C within the framework of MPHD.

Methods

The systematic review protocol was registered in the PROSPERO database (registration number CRD42018111543). Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used to report this systematic review (18).

Participants

Studies in children or adults with CH-C were included. Although CH-C is often diagnosed in childhood, we

allowed studies in adult patients, not only to review cognitive outcome throughout life, but also to prevent exclusion of useful studies for this low-prevalence disease. Studies including CH-C patients as well as other patient groups, for example, CH-T or GHD patients, were only included if CH-C patient data could be extracted separately. If CH etiology was unknown, authors were contacted by email. If the study did not meet the inclusion criteria or the etiology remained unclear, the study was excluded. Since neurocognitive tests allow for comparison to population norm scores, both studies with and without control groups were allowed.

Outcomes

The primary outcomes for this study were cognitive outcome, assessed using full-scale intelligence quotient (FSIQ), and motor outcome. Secondary outcome was QoL. Studies using a validated neurocognitive test, motor test or QoL-questionnaire were included. Regarding motor function, studies with tests for gross and fine motor skills were both accepted.

Studies reporting mean $FSIQ \pm s.d.$ were considered eligible and authors were requested to provide IPD. Patients with an estimated FSIQ, for example, due to failure to complete a test, were not included in IPD meta-analysis.

Study design

Prospective and retrospective cohort studies, case-control studies and other types of observational studies were included.

Study identification and selection

A medical information specialist (JL) performed an exhaustive search in MEDLINE, EMBASE and PsycInfo (all via the OVID interface) from inception to June 11th, 2019, using thesaurus terms (i.e. MeSH-terms in MEDLINE) and textwords. No date or language restrictions were applied. A pilot search revealed that a search for central hypothyroidism and outcomes missed many relevant papers, because origin of disease ('central') or measured outcomes were not explicitly mentioned in title or abstract. Therefore several (sub)searches were constructed:

1. Searches for [A] central hypothyroidism, pituitary dwarfism, hypopituitarism in children; [B] hypothyroidism/thyroid hormone (deficiency) and

pituitary diseases/pituitary hormone (deficiency) and [C] a narrow search for congenital hypothyroidism, were all combined with a search filter for children and a broad search for cognitive, intellectual, motor outcomes and QoL.

2. A narrow search (title or major MeSH) for congenital central hypothyroidism was combined with a child-filter only, not with terms for outcomes.

We cross-checked the reference lists of identified relevant papers in Web of Science and adapted the search in case of additional relevant studies. The bibliographic records retrieved were imported and de-duplicated using Endnote (Clarivate Analytics, Philadelphia, USA; <https://www.endnote.com>). The complete search strategy is shown in Supplementary File 1 (See section on [supplementary materials](#) given at the end of this article). All papers were screened based on title and abstract by two reviewers independently (JCN and LMV). Selected studies were reviewed full text by both reviewers to decide on in- or exclusion. Discrepancies between reviewers were solved by discussion or consulting a third reviewer (NZ). To document the study selection process, references were imported into Covidence online software (Veritas Health Innovation, Melbourne, Australia; <https://www.covidence.org>).

Data extraction

Data extraction from selected studies was performed by two reviewers independently (JCN and LMV), using a pre-specified form. The following variables were included: age, sex, gestational age, (parental) ethnicity, educational status, age at diagnosis, comorbidities (especially MPHD), FSIQ, scores of motor assessment and scores from QoL questionnaires. If IPD could not be obtained from the original publication, authors were contacted via e-mail with a request to share IPD.

IPD were checked for completeness by two reviewers (JCN and LMV). If data were incomplete, original authors were contacted again to provide additional information.

Risk of bias assessment

Risk of bias was assessed with the Newcastle-Ottawa Scale (NOS) for Quality Assessment. Since the NOS is not suitable for cross-sectional studies, adapted scales have been created (19). We adapted the NOS scale for cross-sectional studies for our research question (Supplementary File 2).

Data synthesis and statistical analysis

Statistical heterogeneity between studies was assessed using the E-statistic (energy) test for equality of multivariate distributions. Given the limited power of such tests, a *P* value for the test of heterogeneity <0.10 was considered to indicate a high likelihood of heterogeneity. One-stage IPD meta-analysis was performed, using a linear mixed model with FSIQ as dependent variable. Random intercepts were fitted for each study. Maximum likelihood was used for parameter estimation. Patient characteristics such as age and sex were added to the model as fixed effects, to study the association between age or sex and FSIQ. Fit of the models was compared using the Akaike Information Criterion (AIC) and one-way ANOVA. We planned to compare outcomes between MPHD patients and isolated CH-C patients if both subgroups were represented sufficiently within the dataset. A binomial test was used to compare the number of CH-C patients with an FSIQ below 85 (≥ 1 s.d. below population norm score) or below 70 (≥ 2 s.d. below population norm score) to population norm scores. Descriptive analyses, statistical tests and meta-analysis were performed with RStudio, version 3.6.1 (2019-07-05), using packages energy and lme4 (20, 21, 22).

Results

The literature search yielded 885 unique articles of which 188 articles underwent full text review. The study selection process was performed for each outcome independently; the selection process for FSIQ is shown in Fig. 1. Thirteen studies included CH-C patients, but seven of these studies were excluded because CH-C patient data could not be extracted separately (23, 24, 25, 26, 27, 28, 29). From the study by Bucher *et al.*, only aggregate data could be obtained because original data were no longer available (29). In addition, nine out of 33 patients had an estimated FSIQ which had been 'empirically rated [by authors] based on educational achievement', for example, a patient attending a 'normal school' was assigned an FSIQ of 100 (29). Although remaining FSIQs were measured with validated tests, aggregate data from this study were considered low quality evidence and the study was excluded from meta-analysis.

For the primary outcome FSIQ, six studies were eligible for extraction of IPD (30, 31, 32, 33, 34, 35). Next, all studies identified in the search were screened for the primary outcome motor functioning. However, motor

Figure 1

Study selection process for primary outcome full-scale intelligence quotient, reported using the PRISMA IPD flow diagram.

Abbreviations: CH, congenital hypothyroidism; CH-C, congenital hypothyroidism of central origin; CH-T, congenital hypothyroidism of thyroïdal origin; IPD, individual patient data; IQ, intelligence quotient.

functioning was evaluated in one study only and thus no meta-analysis was performed for this part of the primary outcome. The study selection for motor function is shown in Supplementary File 3.

For the secondary outcome QoL five potentially eligible studies were identified (13, 36, 37, 38, 39). Four studies were excluded because data of CH-C patients could not be obtained separately. IPD on QoL could be retrieved from one study only (39). An overview of eligible studies for which authors did not provide IPD is presented in Supplementary Table 1. The complete risk of bias assessment is shown in Supplementary Table 2.

Study characteristics

IPD regarding the primary outcome FSIQ was obtained from six studies: Pollitt *et al.* (30), Rosenbloom *et al.* (32), Frankel *et al.* (31), Rosenbloom *et al.* (32), Meyer-Bahlburg *et al.* (33), Karges *et al.* (34) and Kempers *et al.* (35). Characteristics of included studies are presented in Table 1.

In total, 30 CH-C patients (20 males) were eligible for inclusion in IPD meta-analysis (Table 2). Age of the included patients ranged from 3 to 21 years, with a mean age of 12.9 ± 4.3 years. The majority of patients had MPH (27/30, 90%). Information regarding age at start of

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Table 1 Overview of studies eligible for meta-analysis.

Reference	Country	Design	Patient group (n, n of CH-C patients)	Patient characteristics (sex and age range)	Control group	Outcome measured; instrument used	Patients included in IPD-meta-analysis, n
Pollitt <i>et al.</i> (30)	USA	CSS	GHD: 15, including MPHD with CH-C: 5	M: 2/F: 3; 8–15 y	NA	Intelligence; WISC	5
Rosenbloom <i>et al.</i> (32)	USA	CSS	Hypopituitarism: 10, including CH-C: 5	M: 2/F: 3; 14–18 y	NA	Intelligence; Stanford-Binet test (form L-M)	5
Frankel <i>et al.</i> (31)	Israel	CSS	Hypopituitarism: 39, including CH-C: 10	M:7/F:3; 4–20 y	NA	Intelligence; WISC (n = 6) or WAIS (n = 2)	8
Meyer-Bahlburg <i>et al.</i> (33)	USA	CSS	GHD: 29, including MPHD with CH-C: 4	M: 4; 3–21 y	NA	Intelligence; WPPSI (n = 1), WISC (n = 2) or WAIS (n = 1)	4
Karges <i>et al.</i> (34)	Germany/ Portugal	CSS	Isolated CH-C: 6	M: 3/F: 3; 1–16 y	NA	Intelligence; K-ABC (n = 1), other (n = 2)	3
Kempers <i>et al.</i> (35)	the Netherlands	CSS	CH: 87, including CH-C: 5	M:4/F:1; 10 y	NA	Intelligence and motor functioning; WISC-R and MABC	5

Frankel *et al.* included ten patients with CH-C of which only eight patients were included in the dataset because FSIQ could not reliably be measured in two patients. Karges *et al.* reported on development of six patients with isolated CH-C due to a *TSH β* gene mutation. Global development was described for all patients; FSIQ was measured in three patients which were included in IPD meta-analysis.

CH-C, congenital hypothyroidism of central origin; CH-T, congenital hypothyroidism of thyroidal origin; CSS, cross-sectional study; FSIQ, Full-Scale Intelligence Quotient; GHD, growth hormone deficiency; IPD, Individual Participant Data; K-ABC, Kaufman assessment battery for children; MABC, Movement Assessment Battery for Children; MPHD, multiple pituitary hormone deficiency; NA, not available; WAIS, Wechsler Adult Intelligence Scale; WISC(-R), Wechsler Intelligence Scale for Children(-revised); WPPSI, Wechsler Pre-school and Primary Scale of Intelligence.

treatment, i.e. early (up until the age of 3 months) or late (after the age of 3 months), was available for 13 patients from three studies (32, 34, 35). In seven out of 13 children levo-thyroxine (LT4) treatment was started before the age of 3 months (Table 2).

Meta-analysis full-scale intelligence quotient

A wide range in FSIQ was seen, including scores from 64 to 123 (Fig. 2). Mean FSIQ and s.d. were calculated for each included study: Pollitt *et al.* (30) 96 ± 11.8 , Rosenbloom *et al.* (32) 105 ± 14.4 , Frankel *et al.* (31) 81 ± 15.7 , Meyer-Bahlburg *et al.* (33) 110 ± 13.1 , Karges *et al.* (34) 92 ± 25.7 and Kempers *et al.* (35) 99 ± 5.2 . An FSIQ below 70 (≥ 2 s.d. below the norm score) occurred in 10% of patients, which was more often than the expected 2.3% occurrence in the general population ($P=0.03$, 95% CI for true probability 3–100%). An FSIQ below 85 (≥ 1 s.d. below norm score) was found in 27% of patients. This was also more frequent than the expected 15.9% occurrence in the general population, but the difference was not statistically significant ($P=0.09$, 95% CI of true probability 14–100%).

To assess homogeneity across included studies the multi-sample E-statistic (energy) test for equal

distributions was performed, which indicated a high level of heterogeneity ($P=0.06$) (21). The use of a linear mixed model was therefore considered appropriate.

Mean FSIQ for all patients included in the meta-analysis was 97 (95% CI: 88–105). Mean FSIQ in male patients was 95 (95% CI: 84–106), while female patients had a mean FSIQ of 99 (95% CI: 91–108). However, adding sex to the model as a fixed effect showed that this difference was not statistically significant (95% CI: –17.4 to 5.2; $P=0.3$). Adding age to the model as a fixed effect did not improve the fit of the model (95% CI: –2.3 to 0.2; $P=0.10$).

Comparing FSIQ between early and late treated patients was not possible since information regarding age at start of treatment was missing for the majority of patients. A comparison between patients with or without MPHD could not be performed because patients with isolated CH-C were underrepresented in our dataset (only three out of 30).

Because a high level of heterogeneity among included studies was noted (Fig. 2), a sensitivity analysis was performed by omitting the study from Frankel *et al.* (31). In the remaining patients ($n=22$) a mean FSIQ of 101 (95% CI: 95–106) was found. While excluding data from Frankel *et al.* does not change the overall conclusion –

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Table 2 Overview of patients included in individual patient data meta-analysis.

Reference	Patient no.	Sex	Age at treatment initiation (months)	Presence of MPHD			Age at test (y)	IQ		
				GHD	ACTH	GND		Full-scale	Performat	Verbal
Pollit <i>et al.</i> (30)	1	F		+			15	84	84	87
	2	F		+			13	88	82	97
	3	M		+			8	91	103	80
	4	F		+			9	104	97	110
	5	M		+			12	112	108	114
Rosenbloom <i>et al.</i> (32)	6	F	18	+			14	115		
	7	F	11	+			15	100		
	8	F	8 y	+			16	101		
	9	M	5 y	+			17	86		
Frankel <i>et al.</i> (31)	10	M	12	+			18	123		
	11	M		+	+	+	13	67	63	78
	12	M		-	-	+	15	74	75	78
	13	M		+	-	+	19	83	80	89
	14	F		+	-	+	20	72	71	77
	15	M		+		+	15	89	103	76
	16	F		+	-		7	113	97	128
	17	M		+			10	84	74	99
	18	M		+	-	+	14	64	71	64
Meyer-Bahlburg <i>et al.</i> (33)	19	M	>3 [†]	+	-	-	13	92		
	20	M	>3 [†]	+	-	+	21	123		
	21	M	>3 [†]	+	+		3	110		
	22	M	>3 [†]	+	-		8	115		
Karges <i>et al.</i> (34)	23	F	1 day	-	-	-	5	119		
	24	M	3	-	-	-	16	68		
	25	M	4	-	-	-	8	88		
Kempers <i>et al.</i> (35)*	26	M	1	+	+		10	92	92	94
	27	F	0.5	+	+	+	10	96	88	107
	28	M	2	+	+		10	103	103	102
	29	M	0.5	+	+	+	10	105	103	106
	30	M	1	+	+	+	10	99	97	102

For blank cells, no data were available.

* Study provided results of magnetic-resonance imaging (MRI): hypoplasia of the pituitary in patients 18–21 and ectopic posterior pituitary and interrupted pituitary stalk in patients 18–22. [†]Estimation based on start of growth hormone treatment; exact age at which central hypothyroidism was diagnosed could not be obtained;

ACTH, adrenocorticotrophic hormone deficiency; GHD, growth hormone deficiency; GND, gonadotrophic hormone deficiency; IQ, intelligence quotient; MPHD, multiple pituitary hormone deficiency.

mean FSIQ and 95% CI remain within population norm scores – the sensitivity analysis does indicate this study is driving the tendency toward a lower FSIQ.

Motor outcome

Motor outcome was assessed in one study. Kempers *et al.* used the Movement Assessment Battery for Children to evaluate motor outcome in five CH-C patients included in their study (35). Among these patients, one had a normal total motor impairment score, indicating no motor problems. Four had an abnormal score, indicating borderline motor problems in one patient and definite motor problems in three patients. All CH-C patients in this study had MPHD and had treatment started before the age of 2 months.

Secondary outcome: quality of life

For the secondary outcome QoL, data from one study could be obtained. Joustra *et al.* studied health-related QoL in 15 adult male patients with isolated CH-C caused by *IGSF1* deficiency syndrome using the Short Form-36 (SF-36) questionnaire (39). When compared with 191 healthy controls, no significant differences were found.

Discussion

To our best knowledge, this is the first systematic review reporting on cognitive outcome in CH-C. Information on primary outcome FSIQ could be obtained from 30 patients (three isolated CH-C; 27 CH-C within the framework of MPHD) from six studies. Although the FSIQ in CH-C

Figure 2

Box-plot of the full-scale intelligence quotient in CH-C patients included in individual patient data meta-analysis. Lower and upper box limits represent 25th and 75th percentile; line in the box represents the median; lower and upper error bars represent the minimum and maximum value, except for study III, where the maximum value is represented by a dot.

Horizontal reference area displays mean FSIQ in general population, with 25th and 75th percentile. Study numbers: I, Pollitt *et al.*; II, Rosenbloom *et al.*; III, Frankel *et al.*; IV, Meyer-Bahlburg *et al.*; V, Karges *et al.*; VI, Kempers *et al.*

Abbreviations: CH-C, congenital hypothyroidism of central origin; FSIQ; full-scale intelligence quotient.

patients (mean: 97, 95% CI: 88–105) is comparable to the population norm score (mean FSIQ: 100, s.d. 15), a wide FSIQ range was seen, which appeared to be shifted toward lower values. An FSIQ below 70 (≥ 2 s.d. below norm score) occurred significantly more often in CH-C patients than would be expected in the general population.

Since age at start of treatment was unknown for the majority of patients, we could not compare early and late treated CH-C patients. Furthermore, a reliable comparison between isolated CH-C and MPHD patients was not possible, as the majority of patients had MPHD. The underrepresentation of isolated CH-C patients was not unexpected since it has been reported that 66–98% of CH-C patients have MPHD (10, 40, 41). This reflects clinical practice in countries using a neonatal screening method that detects CH-C, where most detected patients have MPHD and only a minority has isolated CH-C (6, 7, 40).

Previous studies have suggested that cognitive outcome in CH-C patients, especially those with MPHD,

may be impaired. Nebesio *et al.* performed a large, retrospective study in 42 CH-C patients (98% MPHD) (41). Clinical characteristics were evaluated, including the presence of developmental delay. Medical charts were used to assign developmental delay, which was based on parental report, visits to a developmental pediatrician or involvement in early intervention therapies (personal communication with author). Developmental delay was seen in 50% (21/42) of the patients. When comparing patients detected in neonatal screening to those detected clinically later in life, developmental delay was seen in 25% (2/8) of early-detected versus 56% (19/34) of late detected patients. Early-detected patients had a mean time to endocrine consultation of 4.6 months, while late-detected patients had a mean time to endocrine consultation of 16.9 months (41). While this is the only study comparing early versus late treated CH-C patients with regard to developmental outcome, the study was excluded during the study selection because no validated neurocognitive test was used (Fig. 1).

Brown *et al.* reported a below average FSIQ in 10 children with congenital hypopituitarism (seven with MPHD including CH-C, three with isolated GH deficiency) (27). Mean FSIQ in these patients was 75 (95% CI: 70–80). Since the patient group also included three cases of isolated GHD and original data were no longer available, data on CH-C patients could not be extracted separately (personal communication with author). The study was therefore not eligible for our meta-analysis (Supplementary Table 2). It is interesting to note that all seven cases of MPHD had hypoglycemia at initial presentation which may have influenced brain development.

Bucher *et al.* studied intellectual and school performances of 33 late-treated CH-C patients, all with MPHD (29). Intelligence was measured using a validated test in most patients, but nine out of 33 patients had an estimated FSIQ based on their educational level. A patient attending a 'normal school' was assigned an FSIQ of 100, while patients attending college or university were assigned FSIQs of 115 and 125, respectively (29). While the study reported a mean FSIQ of 103, this average must be interpreted with caution since an objective measurement was lacking in almost one-third of patients.

Beside the rather general concept of FSIQ, several components of cognitive functioning can be distinguished, for example, executive functioning, memory and visuospatial processing. Studies of such components in CH-C are sparse, only one study could be identified. Joustra *et al.* studied executive functioning and memory in 15 adult male patients with isolated CH-C, due

to *IGSF1* deficiency (39). Patients were compared to 54 healthy controls. The study results suggest a mild deficit in attentional control in isolated CH-C patients, while no differences were found regarding memory (39). Although *IGSF1* deficiency patients form a specific subgroup, *IGSF1* deficiency is the most common genetic cause of isolated CH-C and these results support the need for further research on specific cognitive functioning domains in all CH-C patients (42).

In summary, corresponding with findings from our meta-analysis, previous studies not included in this meta-analysis also suggest cognitive impairment in CH-C patients. However, no firm conclusion can be drawn from these studies, due to the lack of validated tests and separate data on CH-C patients.

There are various reasons to expect impaired cognitive outcome in children with MPHD. First, MPHD may lead to hypoglycemia during the neonatal period, potentially causing brain damage and developmental disability later in life (40). Furthermore, neonatal thyroid hormone concentrations are known to be significantly lower in MPHD patients compared with isolated CH-C patients, and more severe CH has been associated with lower IQ scores (43, 44). Still, the presence of additional hormone deficiencies makes it difficult to delineate the precise role of thyroid hormone deficiency in the cognitive outcome in this subgroup of patients. It is expected, though, that CH-C patients benefit from early treatment for both their hypothyroidism and additional hormone deficiencies. Therefore, adding detection of CH-C to more neonatal screening programs has been suggested (45, 46). Unfortunately, this systematic review does not answer the question whether early detection of CH-C is superior to clinical case detection with regard to cognitive outcome.

Besides cognition, motor function is also known to be impaired in children with severe CH-T and this impairment is associated with CH severity (14, 47). Because CH-C patients have moderate-to-severe hypothyroidism in more than half of the cases (9), motor function was systematically reviewed as well, but only one study examined this. Kempers *et al.* studied motor function in 5 CH-C patients with MPHD, obtaining a score for manual dexterity, ball skills and balance (35). Motor impairment was seen in 4 out of 5 patients; all four patients had needed physical therapy during childhood. Despite the small sample size, these results indicate that clinical attention to motor function is necessary, and that further studies examining motor function in pediatric CH-C patients are needed.

A strength of the current study is the number of included CH-C patients, despite the low prevalence of the disease. Although 30 patients is still a small number, it is the largest group studied with validated tests until now. In addition IPD-meta-analysis could be performed, which allows detailed exploration of characteristics at the individual patient level (in this study age and sex), when compared with aggregate data meta-analysis (48). Finally, although various tests were used to assess FSIQ across the included studies, four out of six studies used a Wechsler test (Table 1). The remaining studies used the Stanford-Binet test and Kaufman Assessment Battery for Children (K-ABC). Notwithstanding the variety in tests, we treated FSIQ as a homogeneous outcome given the generally high correlation of FSIQ across intelligence tests (49, 50).

Several limitations of the current study can be identified. Although information on additional hormone deficiencies was available, information on severity of hypothyroidism and age at treatment initiation was lacking for the majority of patients. In addition, while the used intelligence tests were homogeneous across studies, heterogeneity was seen on other levels. For instance, there was a wide range in publication dates of the included studies. Because we aimed to identify all available studies, no date restriction was applied. The wide range in publication dates may have led to clinical variability among patients, for example, in treatment received, as guidelines for CH-C have been established only recently (11). Another important point is selection bias. Pollitt *et al.* studied intelligence in some of the first pediatric patients receiving GH, stating that ‘preference was given to patients who the pediatricians thought were well-adjusted psychologically, and who also had cooperative parents, [so] that the program of treatment would be adhered to as scheduled’ (30). This may have led to overestimation of the FSIQ and FSIQ range. Frankel *et al.* mainly included children from primarily Jewish oriental families (31). It has been assumed that these families were first generation immigrants, ‘expected to perform poorly on culturally biased intelligence tests’ (33). This might explain the results from the sensitivity analysis, showing a tendency toward a higher mean FSIQ when excluding results from Frankel *et al.*

With these limitations in mind, it remains unknown whether early detection of CH-C is superior to clinical case detection regarding cognitive outcome. To answer the question whether cognitive outcome differs between early and late treated CH-C patients, additional well-designed and sufficiently large studies are needed.

In the Netherlands CH-C is detected through neonatal screening (3). We are currently performing a nationwide follow-up study on cognitive outcome in more than 80 early treated Dutch CH-C patients. In this study, we are including CH-C patients born between 1995 and 2015, detected through neonatal screening and able to complete an age-specific intelligence test. Results from this ongoing study will provide more evidence on cognitive outcome in patients with early treated CH-C. Meanwhile, studies determining cognitive outcome in late treated, clinically detected CH-C patients are needed as well, in order to subsequently compare early and late detected patients.

In conclusion, we report a mean FSIQ of 97 in a group of 30 CH-C patients studied with IPD meta-analysis. An FSIQ below 70 was found in 10% of CH-C patients. Although the current systematic review provides an overview of published data on cognitive outcome in CH-C patients, results should be interpreted with caution due to the relatively small group of patients, heterogeneity of the study populations and missing data on disease severity and initiation of treatment. In order to obtain a complete overview of cognitive outcome in CH-C patients and answer the question whether early detection and treatment improves cognitive outcome, well-designed and sufficiently large studies are needed, including both isolated CH-C patients and MPPH patients with CH-C, as well as early and late detected patients.

Supplementary materials

This is linked to the online version of the paper at <https://doi.org/10.1530/EJE-19-0874>.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this study.

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A S van Trotsenburg and N Zwaveling-Soonawala: contributed equally to this work.

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